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Commentary

ADAURA: Mature Enough for Publication, Not for Prime Time

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Disclosures of potential conflicts of interest may be found at the end of this article.

In oncology, the goal of a new treatment is to make patients live longer and/or better. It is disconcerting that many drugs were approved by regulatory bodies without meeting either of those endpoints [1]. This alarming aspect is coupled with the skyrocketing price of new molecules, spreading a well-known side effect: financial toxicity.

A common argument against overall survival (OS) as the primary endpoint, in particular, in the adjuvant setting is the time required for results. So, to shorten this waiting time, surrogate endpoints, such as disease-free survival (DFS), have been adopted with the idea that a positive trial for DFS, particularly in case of huge benefit, will ultimately yield an OS benefit. Speeding up the process could benefit patients, exposing them earlier to a new molecule. Conversely, in the absence of a correlation with improved OS, the use of adjuvant therapy in this situation turns a person into a patient. Indeed, if there is no improvement in OS, the patient might as well take the drug at the time of disease relapse when the motivation for treatment, and potential to improve symptoms despite possible side effects, is stronger.

No recent example illustrates these challenges better than the ADAURA trial [2].

It is a randomized phase III trial comparing adjuvant osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), with placebo in patients with resected stage IB-IIIA EGFR-mutated non-small-cell lung cancer (NSCLC). Fifty-five percent of patients also received standard adjuvant chemotherapy. It was presented during the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2020. Recently published data [2] were from an unplanned interim-analysis (mature data were expected for February 2023) prompted by the data safety monitoring board, which advised, given the efficacy signal, to unblind the study.

In the trial, osimertinib improved the relative risk of DFS by 83% versus placebo ($p < .0001$) in patients with stage II to IIIA disease; the 2-year DFS was 90% with osimertinib versus 44% with placebo. In the overall study population of stage IB to IIIA NSCLC, osimertinib improved the relative risk of DFS by 79% versus placebo ($p < .0001$), with 2-year DFS rates of 89% vs 53%, respectively. The impressive DFS benefit has convinced many oncologists to consider using this therapy before OS data are available.

This is not the first adjuvant trial to show superior DFS. The single-arm phase II SELECT trial involved 2 years of adjuvant erlotinib in stage IA-IIIA EGFR+ NSCLC. The 2-year DFS was 88%, whereas it dropped to 56% at 5 years, although OS remained high, at 86% [3]. The phase III CTONG1104 trial compared 2 years of adjuvant gefitinib with standard chemotherapy in stage II-IIIA EGFR+ NSCLC. It showed a DFS advantage for gefitinib with a hazard ratio (HR) of 0.60 [4], although final results presented at ASCO 2020 did not find an OS advantage. Any numerical advantage was further marred by the fact that 50% of patients in the chemotherapy arm never received any EGFR-targeted therapy upon progression. The phase II EVAN trial, assessing adjuvant erlotinib compared with chemotherapy in stage IIIA EGFR+ NSCLC, found a DFS decrease with a 2-year relative risk of relapse of 1.82 in the standard arm [5]. The authors concluded it is promising but that mature OS data are needed.

Currently, the only mature OS data we have with TKIs for the EGFR-mutated NSCLC come from the above-mentioned CTONG1104 phase III trial, which showed a nonsignificant HR for death of 0.92 (95% confidence interval [CI], 0.62–1.36; $p = 0.674$) for gefitinib versus cisplatin-vinorelbine, corresponding to a 2.1% nonsignificant survival improvement in favor of chemotherapy [4].

ADAURA was designed with DFS as the primary endpoint, with superiority defined as an HR of 0.70 for stage II–IIIA. Adjuvant chemotherapy was not mandatory, nor was it a stratification factor. Nearly half the patients did not receive adjuvant chemotherapy, with 25%–28% receiving adjuvant chemotherapy in stage IB, and 70%–73% in stage II and 81%–78% in stage IIIA for the placebo and osimertinib arms, respectively.

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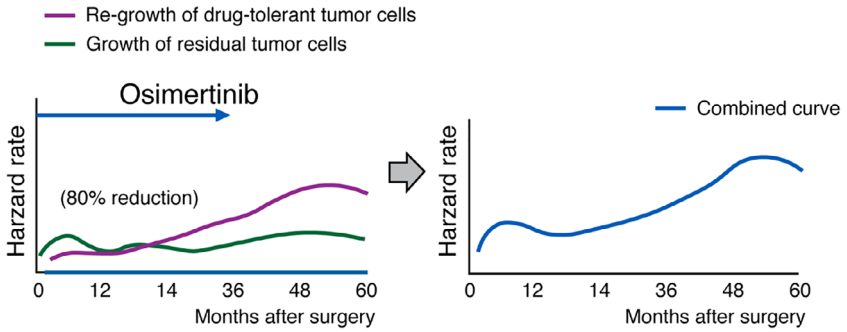

Figure 1. Hypothetical influence of adjuvant osimertinib on tumor growth (adapted from Suda [10]): at first, osimertinib will decrease the growth of residual tumor cells, but in parallel, drug-tolerant cells will emerge, leading to increased relapses starting later in the adjuvant therapy phase.

A prespecified exploratory analysis in ADAURA was the assessment of the sites of recurrence (including the central nervous system; CNS) and the time to CNS disease recurrence. Overall, the HR for CNS disease recurrence or death was 0.18 (95% CI, 0.10–0.33), indicating an 82% reduction in the risk of CNS disease recurrence or death with osimertinib.

Osimertinib is known to have excellent CNS activity and penetration, clearly superior to first- and second-generation TKIs [6] and to chemotherapy, so these data come as no surprise. However, two aspects have to be highlighted. First of all, the data are immature, with only 7% maturity for CNS events; hence, drawing firm conclusions is imprudent. The second issue is the choice of brain imagery for screening. Computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI) were both possible options. It has long been known that MRIs are far superior to CT scans to detect brain metastases [7]. The information about the number of patients who had a CT scan instead or brain MRI is not available [2], creating a possible imbalance between arms, hence representing an important confounding factor to interpret the primary endpoint. The use of CT scans leads to potential understaging of patients who are in fact already metastatic. These patients would consequently be undertreated in the control arm, as patients with CNS metastases would normally receive osimertinib as standard therapy.

What we have described so far concerns trial design and data interpretation. The missing ring of the chain is the biological rationale for giving osimertinib for 3 years. The authors justify this first by analogy with imatinib, a targeted tyrosine kinase inhibitor, used as an adjuvant treatment following complete gross resection of Kit (CD117)-positive gastrointestinal stromal tumors (GISTs), which improved DFS and final OS if taken for 3 years instead of 1 year [8]. Although this is intriguing, we struggle to fully understand the analogy, as GIST biology and mechanisms of progression are completely different from those of EGFR-mutated lung adenocarcinoma.

Next, the authors highlight that in the single-arm prospective SELECT [3] study, which evaluated erlotinib as a 2-year adjuvant treatment in patients with completely resected EGFR-mutated NSCLC, although recurrences were rare on erlotinib, most occurred in the 12 months after discontinuation. This suggests that a longer duration of adjuvant treatment may be beneficial. Similar findings emerged in the CTONG1104 ADJUVANT [4] trial. Gefitinib showed an advantage over chemotherapy in treatment failure patterns, especially in extracranial metastases. The first peak of extracranial metastases appeared at 9 –15 months in the chemotherapy arm compared with 24–30 months with gefitinib. With gefitinib, the first metastatic site was the CNS (29 of 106 [27.4%]) [9] and the peak of CNS metastases post-surgery occurred at 24 to 36 months, raising the question about a longer duration of TKI therapy.

In contrast, it is rather complicated to identify a biological mechanism through which a TKI in oncogene-driven cancer could kill micrometastases, whether with 1, 3, or more years of therapy. As thoughtfully discussed in an editorial by Dr. Suda [10], by using EGFR-TKI in the adjuvant setting, the height of the hazard rate of recurrence will be lower than what we see with chemotherapy. However, the hazard rate curve for regrowth of drug-tolerant cells will likely be higher with a continuous increase during the observation period. Using a more potent TKI, such as osimertinib, may potentially reduce tumor cell regrowth, including CNS recurrence, and prolong DFS but inevitably increase the development of drug-tolerant cells over time (Fig. 1). This might result in clonal resistance selection and on-therapy, untargetable progression with no real survival benefit.

If the goal of an adjuvant trial is to increase survival and improve patients' quality of life while waiting for mature OS data to be available, we should not adopt osimertinib as a standard adjuvant treatment.

Recently, the U.S. Food and Drug Administration granted osimertinib a priority review designation to a supplemental new drug application [11] based on what we consider, although statistically and formally positive, a suboptimal endpoint (DFS).

We fear that this trial will not necessarily represent a step forward, but rather a missed opportunity to better treat our patients with NSCLC harboring EGFR mutations.

Disclosures
The authors indicated no financial relationships.

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Editor's Note:
See the related commentary, "Adjuvant Osimertinib: A New Standard of Care" by Michael J. Jelinek and Charu Aggarwal on page 263 of this issue.